

Objectives

- ❖ Parametric quantification of diabetes progression to diabetic nephropathy through time-to-event (TTE) analysis.
- ❖ Unlike conventional regression methods, TTE analysis incorporate censoring events and time components providing unbiased and better estimates of survival function.
- ❖ Present study focused on development of TTE model of diabetic nephropathy and evaluating covariates effects (discrete and continuous) on the progression of T2DM to diabetic nephropathy.

Methods

- ✓ Retrospective data of diabetic patients was collected from endocrine clinic of a tertiary care hospital comprising of 251 T2DM patients with a follow-up period of 7.2 years.
- ✓ Parametric TTE analysis was performed using NONMEM software.
- ✓ Event was defined by persistent proteinuria for three consecutive visits.
- ✓ For development of base model; exponential, Gompertz and Weibull hazard model were tested while Stepwise approach was adopted for evaluating covariates effects i.e., univariate analysis followed by multivariate analysis.
- ✓ Likelihood ratio test (LRT) with significance level (α) of 5% was used to discriminate between nested models and a drop of 3.84 with one degree freedom by the addition of covariate with the base model was considered statistically significant ($p > 0.05$).
- ✓ The selection of final model was based on the lowest OFV, Kaplan Meier visual predictive check (KM-VPC) with 100 simulations, relative standard error (RSE) as well as the scientific plausibility.
- ✓ External validation of final model was performed on 109 T2DM patients.

Results

Out of 251 patients, 96 (38%) patients developed proteinuria. The best base model was Gompertz hazard model ($h(t) = \lambda_0 \cdot e^{\beta \times t}$) with the baseline hazard of 1.006 /year (RSE=53%) and shape (probability density function) of 2.6671 (RSE=9%). The hazard of developing proteinuria decreases with increase in estimated glomerular filtration rate above 85.20 ml/min/1.73m² (HR=0.959; 95% CI [0.975-0.942]) while increase in fasting blood sugar over time above 7.4 mmol/L increase the hazard of developing proteinuria (HR=1.258; 95% CI [1.139-1.389]). Similarly, the increase in systolic blood pressure over time above 132 mmHg increase the risk of developing proteinuria in diabetic patients (HR=1.073; 95% CI [1.043-1.103]).

$$H(t) = \lambda_0 \cdot \exp [(SHP*(TIME) (\theta_{SBP} * (SBP-132) + \theta_{FBS} * (FBS-7.4) + \theta_{EGFR} * (EGFR-85.20))$$

Conclusions

- eGFR trend can be useful indicator for early detection of diabetic nephropathy while proper management of systolic blood pressure and fasting blood sugar may further help in minimizing the risks of developing diabetes associated proteinuria.
- The development of TTE model in present study may help in generating new knowledge on underlying mechanism of progression of diabetes to diabetic nephropathy by evaluating patients and disease data over time.
- These approaches may help in improving treatment strategies by improving the understandings of medical practitioner about the disease progression over time.

Parameter	Description	Typical Value	Relative estimation error (RSE%)
λ_0	Baseline hazard at time of enrolment	0.0006	53%
ALPHA	Shape parameter	0.981	9%
θ_{SBP}	Effects of SBP on hazard	0.067	14%
θ_{FBS}	Effects of FBS on hazard	0.263	13%
θ_{EGFR}	Effects of EGFR on hazard	-0.0327	24%

Table 1. Estimated parameters in the final model

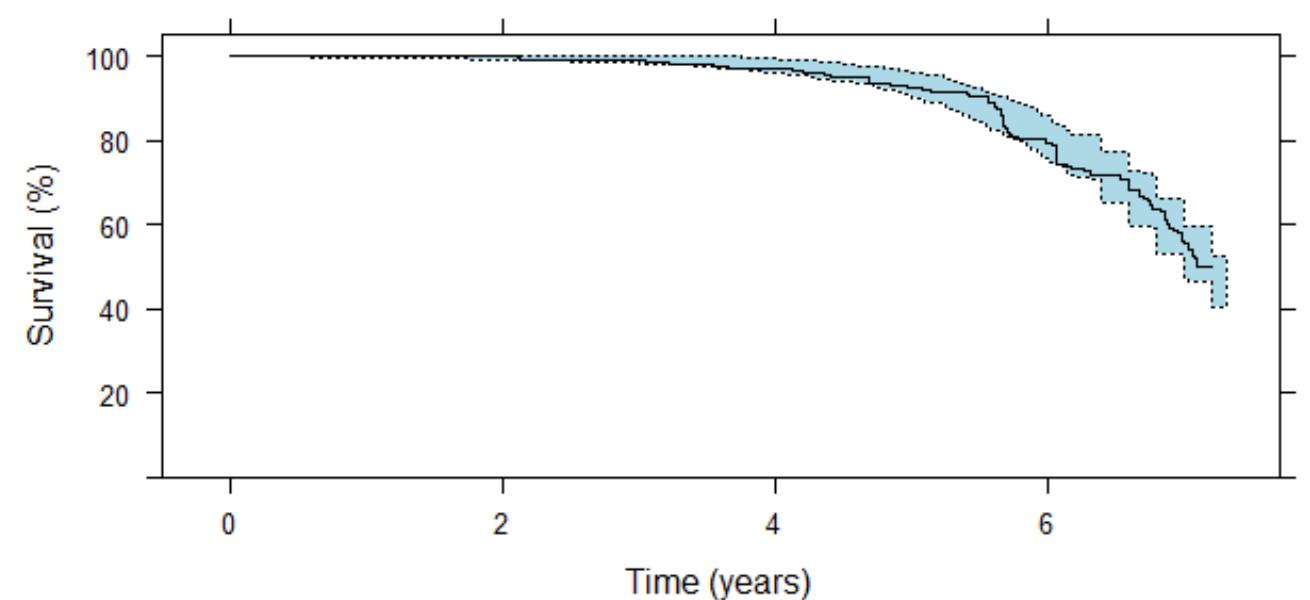


Fig 1. Visual Predictive Check (VPC)

Based on the VPC, the 95% confidence interval of the median, 10th and 90th percentiles of the simulated data (shaded in blue), have overlaid the median, 10th and 90th percentile of the observed data, implying the good predictive performance of the final model as seen in Figure 1.

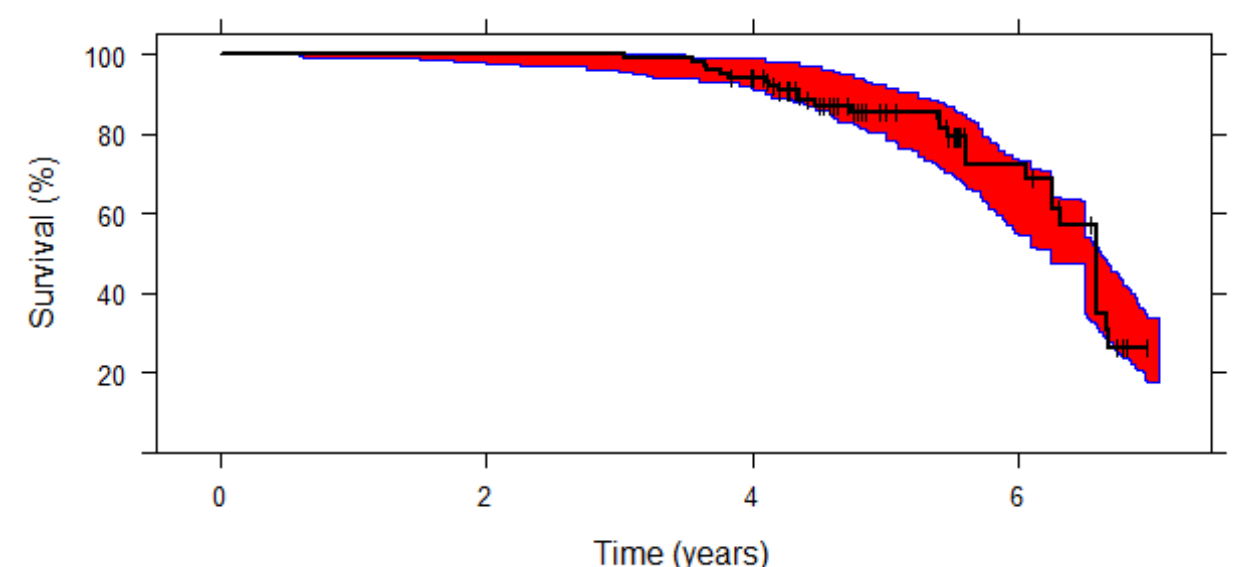


Fig 2. External Validation Visual Predictive Check (VPC)

References

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